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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/791,093

03/01/2004

John Bryan Jones

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EXAMINER

MOORE, WILLIAM W

ART UNIT

PAPER NUMBER

1656

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DELIVERY MODE

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/791,093	<b>Applicant(s)</b> JONES ET AL.	
	<b>Examiner</b> WILLIAM W. MOORE	<b>Art Unit</b> 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 21 December 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-62 is/are pending in the application.
- 4a) Of the above claim(s) 21-62 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-12 and 15-18 is/are rejected.
- 7) ☒ Claim(s) 13, 14, 19 and 20 is/are objected to.
- 8) ☒ Claim(s) 21-62 are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>20040816</u> .  | 6) <input type="checkbox"/> Other: _____                          |

## DETAILED ACTION

*Priority*

Applicant's claim in the Declaration of Inventorship and in the first page of the specification filed 1 March 2004 to priority under 35 U.S.C. § 119 of the 10 November and 21 December, 1998 filing dates of, respectively, the US provisional applications Nos. 60/107,758 and 60/113,061, is hereby acknowledged. In responding to this communication, Applicant is invited to amend lines A-D of page 1 of the specification to revise the continuing data for the instant application by including the status, including the filing date, of the parent, intervening, US application serial No. 09/436,513, not yet cited in the chain of priority.

*Information Disclosure Statement*

Applicant's Information Disclosure Statement [IDS] filed on 16 August 2004 is hereby acknowledged. All references cited therein were cited and supplied in the parent US application serial No. 09/436,513. One document, C75, a selection from a products catalogue, is lined-through because no date for its publication is provided, or evident in the pages provided, thus it cannot comply with the requirements of MPEP § 609.

*Election/Restrictions*

Applicant's election without traverse of the invention of cysteine-modified subtilisin of Group II, claims 1-20, at page 12 of the reply filed on 21 December 2007 is acknowledged, as is the further election of the species of cysteine-modified subtilisins wherein cysteine is substituted for an amino acid present at the S<sub>1</sub> subsite position **156** as numbered by correspondence with the amino acid sequence of the mature subtilisin BPN'. Claims 1-20 are examined herein, in part, to the extent that they read upon a cysteine-modified subtilisin of Group II and, in particular the elected species and claims 1-20 are withdrawn, in part, from further consideration to the extent that they are drawn to non-elected cysteine-modified proteases of Groups I and III, and claims 21-62 are withdrawn entirely from further consideration as drawn to a non-elected invention.

*Objection to the Specification*

- A. At page 10, line 29, the specification states a spurious reference - "Rick to provideall serine hydrolase" - followed on the same line by a misspelling of the word "including". The word "subtilisin" is misspelled at page 11, line 13,
- B. This application contains numerous references to particular amino acid positions, e.g., N62, S156, S166, L217, and M222, characterized, e.g., at page 11, line 13, as occurring in a *Bacillus lentus* subtilisin. Such characterization is erroneous where the designated amino

Art Unit: 1652

acids, which are modified by cysteine substitutions according to the specification and claims, do not occur at these positions in the 269-amino acid sequences of the three most commonly modified *B. lentus* subtilisins and instead occur at the stated positions in the 275-amino acid sequence of the native *Bacillus amyloliquefaciens* subtilisin. An appropriate characterization of such positions is found at page 12, lines 11-12, of the specification: "where the numbered positions correspond[s] to [positions in the amino acid sequence of a] naturally occurring subtilisin from *Bacillus amyloliquefaciens*". No Sequence Disclosure according to 37 CFR 1.821 - 1.825 can be required where no amino acid sequence is disclosed in the text of the specification or claims, or in the Drawing Figures, but the specification and the claims – which are part of the disclosure of the specification – must be amended to insert the phrase "where these positions are numbered by correspondence with positions in the amino acid sequence of *Bacillus amyloliquefaciens* subtilisin" at those instances in the specification and claims where reference is made to any of the "amino acid[s]" or "position[s]" 62, 156, 166, 217 and 222. See e.g., page 3, lines 27-28, page 4, lines 14-15, page 6, line 1, page 9, lines 14 and 16, page 11, lines 13-16 and lines 25-26, page 24, lines 21-24, page 25, lines 6-12, and claims 10 and 16.

- C. There is no description of Figure 1 at page 9 in the Drawing Description and the description of Figure 6C states "217C" but should instead state "L217C".

*Claim Objections: Claims Withdrawn From Consideration*

Claims 13 and 59 are objected to, and are withdrawn from consideration herein, because they improperly refer a Drawing Figure, **Figure 2**. Such reference is improper because patent claims should be as complete as possible in themselves and not incorporate references to a figure (see MPEP 2175.05(s)). In addition this reference is misleading where the Figure does not "consist of" a group of substituents only; neither does the Figure properly present any list of substituents. These claims may either be deleted or amended to provide a particular listing of individual, distinct, compounds in a proper Markush format.

*Claim Objections: Informalities*

Claims 1-62 are objected to because of the following informalities:

1. All claims are now presented as center-aligned paragraphs, producing several problems that will make preparation of the claims by the printer for publication difficult and will impede the ready comprehension by the public of the intended subject matter. All claims must be amended to be left-aligned paragraphs and each of the fourteen compounds stated in

Art Unit: 1652

claims 14, 20, and 60 must be presented on separate lines and indented so that each may readily be distinguished.

2. Claims 12 and 58 incorrectly recite "a disaccharides" on line 2, which should be singular.
3. The recitations of the terms ".sub." and ".sup." in claims 8, 10, 11, 15, 17, 37, 54, 56, and 57 to designate subsites, alkyl groups, and ions may confuse the printer and public. Claims 8, 10, 11, 15, 54, 56, and 57 must either be amended (i) to provide line spacing adequate for introducing subscripts and the descriptions must include the subscripts or (ii) amended to state the terms 1, 2, and 1' directly adjacent to the term S and not as subscripts, e.g., S1, S2, and S1'. Claims 17 and 37 must be amended to provide line spacing adequate for introducing both subscripts and superscripts and descriptions must include the subscripts and superscripts, e.g., in claim 17, "a C<sub>1</sub> to C<sub>15</sub> alkyl", "C<sub>1</sub> to C<sub>15</sub>-SO<sup>3-</sup>", and "C<sub>1</sub> to C<sub>15</sub>-CO<sup>2-</sup>", and in claim 37, "L217C-(CH<sub>2</sub>)<sub>2</sub>".
4. Claim 1 commences with the recitation "[a] modified serine hydrolase" but, at line 2 of the claim, improperly recites "said protease" where the latter term is subgeneric relative to the broad genus of "hydrolases". Consistency in nomenclature is best assured by amending all claims reciting "serine hydrolase", e.g. at least the elected claims 1-14, to delete this term and to instead describe the elected subject matter, a modified subtilisin.
5. Finally, the recitations of the 14 compounds in claims 14, 20, and 60 are fragmented, where unnecessary and misleading hyphenation is introduced by the centered alignment. Each embodiment of the claim must be amended to remove misleading hyphenation, and the misspelling of "phenyl" in the ninth compound must be corrected, thus,

“. . . selected from the group consisting of

(R)-2-methoxy-2-phenyl-ethyl-thiol,

(S)-2-methoxy-2-phenyl-ethyl-thiol,

(R)-2-hydroxy-2-phenyl-ethyl-thiol,

(S)-2-hydroxy-2-phenyl-ethyl-thiol,

N-(3'-thiopropyl)-2-oxazolidinone,

N-(3'-thiopropyl)-(S)-4-phenyl-2-oxazolidinone,

N-(3'-thiopropyl)-(R)-4-benzyl-2-oxazolidinone,

N-(3'-thiopropyl)-(S)-4-benzyl-2-oxazolidinone,

N-(2'-thioethyl)-(R)-4-phenyl-2-oxazolidinone,

N-(2'-thioethyl)-(S)-4-phenyl-2-oxazolidinone,

N-(2'-thioethyl)-(R)-4-benzyl-2-oxazolidinone,

N-(2'-thioethyl)-(S)-4-benzyl-2-oxazolidinone,

N-(3'-thio)-(3aR-cis)-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]-oxazol-2-one, and

N-(3'-thio)-(3aS-cis)-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]-oxazol-2-one.”

Art Unit: 1652

Appropriate correction of each informality indicated above is required, which correction must be extended to any non-elected claims that might remain in a response to this communication.

*Double Patenting: Non-Statutory*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-6, 8-11, and 15-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25, 29, 37 and 38 of U.S. Patent No. 6,277,617. Although the conflicting claims are not identical, they are not patentably distinct from each other because the description of products of the patented claims defines a lesser scope than that defined by the pending claims 1, 3-6, 8-11, and 15-17.

Claims 1, 3-6, 8-10, 15, and 16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,284,512. Although the conflicting claims are not identical, they are not patentably distinct from each other because the description of products of the patented claims defines a lesser scope than that defined by the pending claims 1, 3-6, 8-10, 15, and 16.

Claims 1, 3-6, 8-11, and 15-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6, 10, 11, 14, 15, 18, and 19 of U.S. Patent No. 6,395,532. Although the conflicting claims are not identical, they are not patentably distinct from each other because the description of products of the patented claims defines a lesser scope than that defined by the pending claims 1, 3-6, 8-11, and 15-17.

Claims 1, 3-6, 8-11, and 15-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 8, 11, and 12 of U.S. Patent No.

Art Unit: 1652

6,379,942. Although the conflicting claims are not identical, they are not patentably distinct from each other because the descriptions of the products of the patented claims defines a lesser scope than that defined by the pending claims 1, 3-6, 8-11, and 15-17.

*Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 USC § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-6, 8-12, and 15-18 are rejected under 35 U.S.C. § 102 (a) as being anticipated by Davis et al. 1998, cited in an IDS in the parent application and made of record herewith.

In the interests of compact prosecution, and because corresponding rejections were made in the parent application, this rejection addresses both elected and non-elected species of CMM cysteine mutant subtilisins. Davis et al. 1998 disclose the substitutions S156C in a subtilisin S1 subsite, N62C, in a subtilisin S2 subsite, S166C in a subtilisin S1 subsite, and L217C, in a subtilisin S1' subsite, which positions are numbered by correspondence with positions in the amino acid sequence of *Bacillus amyloliquefaciens* subtilisin, and subsequent MTS-mediated modifications of these four cysteine-substituted subtilisins with various glycosides. See schemes 1-3 at page 9615 and accompanying discussion. While Davis et al. do not state that their chemically modified mutant [CMM] S2 subsite, S1 subsite, and S1' subsite subtilisins are transesterases, transamidases or transpeptidases, and conducted their assays in aqueous solution with a common substrate for measuring proteolysis, their CMM subtilisins inherently have the organic synthetic properties of, at least, transesterification and transpeptidation because they meet structural limitations of the claims and are equally disclosed to be such in the instant specification and because the art recognizes that even subtilisins lacking the chemical modifications of Berglund et al., such as subtilisins used for transesterification and transamidation by Bryan et al. US 5,116,741, made of record herewith, and similar subtilisins used for transpeptidation by Arnold et al. US 5,3136,935, made of record with Applicant's IDS catalyze these organic syntheses in non-aqueous environments with appropriate substrates

Art Unit: 1652

Claims 1-6, 8-11, and 15-17 are rejected under 35 U.S.C. 102 (a) as being anticipated by DeSantis et al. 1998, cited in an IDS in the parent application and made of record herewith.

In the interests of compact prosecution, and because corresponding rejections were made in the parent application, this rejection addresses both elected and non-elected species of CMM cysteine mutant subtilisins. DeSantis et al. 1998 disclose the substitutions S156C in a subtilisin S1 subsite, S166C in a subtilisin S1 subsite, and M222C, in a subtilisin S1' subsite, which positions are numbered by correspondence with positions in the amino acid sequence of *Bacillus amyloliquefaciens* subtilisin, and subsequent MTS-mediated modifications of both cysteines with an alkyl amino group having a positive charge. See Scheme 1's formula "f" at page 5968. While DeSantis et al. do not state that their chemically modified mutant [CMM] S1 subsite and S1' subsite subtilisins are transesterases, transamidases or transpeptidases, and conducted their assays in aqueous solution with a common substrate for measuring proteolysis, their CMM subtilisins inherently have the organic synthetic properties of, at least, transesterification and transpeptidation because they meet structural limitations of the claims and are equally disclosed to be such in the instant specification and because the art recognizes that even subtilisins lacking the chemical modifications of Berglund et al., such as subtilisins used for transesterification and transamidation by Bryan et al. US 5,116,741, made of record herewith, and similar subtilisins used for transpeptidation by Arnold et al. US 5,3136,935, made of record with Applicant's IDS catalyze these organic syntheses in non-aqueous environments with appropriate substrates.

Claims 1-6, 8-11, and 15-17 rejected under 35 U.S.C. 102 (b) as being anticipated by Berglund et al. 1997, cited in an IDS in the parent application and made of record herewith.

In the interests of compact prosecution, and because a corresponding rejection was made in the parent application, this rejection addresses non-elected species of CMM cysteine mutant subtilisins. Berglund et al. 1997 disclose the substitutions N62C, in a subtilisin S2 subsite, and L217C, in a subtilisin S1' subsite, which positions are numbered by correspondence with positions in the amino acid sequence of *Bacillus amyloliquefaciens* subtilisin, and subsequent MTS-mediated modifications of both cysteines with an alkyl amino group having a positive charge. See Table 1 and formula "k" of Figure 1. While Berglund et al. do not state that their chemically modified mutant [CMM] S2 subsite and S1' subsite subtilisins are transesterases, transamidases or transpeptidases, and conducted their assays in aqueous solution with a common substrate for measuring proteolysis, their CMM subtilisins inherently have the organic synthetic properties of, at least, transesterification and transpeptidation because they meet structural limitations of the claims and are equally disclosed to be such in the instant specification and because the art recognizes that even subtilisins lacking the chemical



Art Unit: 1652

modifications of Berglund et al., such as subtilisins used for transesterification and transamidation by Bryan et al. US 5,116,741, made of record herewith, and similar subtilisins used for transpeptidation by Arnold et al. US 5,313,935, made of record with Applicant's IDS catalyze these organic syntheses in non-aqueous environments with appropriate substrates.

Claims 1-6, 8-11, and 15-17 are rejected under 35 USC § 102(e) as being anticipated by Bott et al., US 6,277,617, made of record herewith.

Bott et al. disclose the invention of claims 1, 3-6, 8-11, and 15-17 herein, including the elected species S156C-CMM, in their claims 1-25, 29, 37 and 38. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 USC § 102(e). This rejection under 35 USC § 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 1-6, 8-10, 15, and 16 are rejected under 35 USC § 102(e) as being anticipated by Jones et al. US 6,284,512, made of record herewith.

Jones et al. disclose the invention of claims 1, 3-6, 8-11, and 15-17 herein in their claims 1-8. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 USC § 102(e). This rejection under 35 USC § 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 1-6, 8-11, and 15-17 are rejected under 35 USC § 102(e) as being anticipated by Jones et al. US 6,395,532, and Jones et al., US 6,576,454, both made of record herewith.

Jones et al. '532 and Jones et al. '454 identically disclose the invention of claims 1, 3-6, 8-11, and 15-17 herein in, e.g., their Figures 2 and 3, and Examples 1-5. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 USC § 102(e). This rejection under 35 USC § 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

#### *Conclusion*

Claims 14 and 20 are objected to as being dependent upon a rejected base claim, as well as objected to for informalities but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Art Unit: 1652

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/Nashaat T. Nashed/  
Nashaat T. Nashed, Ph.D.  
Supervisory Primary Examiner  
Art Unit 1652

William W. Moore  
14 March 2007